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FELFE & LYNCH

By Norman H. Stepno

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Thomas S. Parker et al.
Serial No.	:	08/432,691
Filed	:	May 2, 1995
For	:	METHODS USEFUL IN ENDOTOXIN BASED PROPHYLAXIS AND THERAPY

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Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with their duty of disclosure, applicants wish to make the attached references of record in this case.

U.S. Patent No. 5,000,958 to Fountain et al. teaches that liposomes may be used to carry antibiotics. In turn, the antibiotics act against bacteria. The liposomes may contain phosphatidylcholine. There is no mention of neutral lipids in the application.

U.S. Patent No. 4,703,062 to Blackburn et al. teaches that emulsions of medium and long chain triglycerides ("MCTs" and "LCTs" respectively), may be used as nutritional supplements. Amino acids may be included, as per the abstract. There is no teaching in this reference of the claimed invention, nor is there a suggestion of it.

European Patent Application 071 995 to Neimann, et al is not available in English. The abstract reads as follows:

> "Fat emulsion for parental administration. An isotonic, LCT/MCT Emulsion (long chain triglycerides/middle chain triglycerides) for parenteral administration, with a total fat content of from 3 to 30%, and an LCT/MCT ratio (long chain triglyceride/middle chain triglyceride) between 4:1 and 1:4, together with a physiologically safe, alcohol is described wherein the emulsion contains an egg phosphatidyl-emulgator.

There is no mention within the reference of treatment of endotoxemia. The reference does not teach the ratios set forth in the claims.

Cué et al., "Reconstituted High Density Lipoprotein Inhibits Physiologic and Tumor Necrosis Factor α Responses To Lipopolysaccharide in Rabbits", Arch. Surg. 129: 197 (Feb. 1994) describes compositions ("reconstituted particles"), which contain an apolipoprotein, phosphatidylcholine and cholesterol. Various physiological parameters were studied. Endotoxemia was not studied, and the particles, by virtue of the presence of apoAI, do contain peptide.

Glueck et al., "Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglyceridemic women", J. Lab. Clin. Med. 123: 59-64 (1994) is cited solely to show that, at the time of the invention, it was known that high levels of triglycerides were considered toxic, as they lead to conditions such as pancreatitis. See the entire article.

Read et al., "Chylomicrons Enhance Endotoxin Excretion in Bile", Infect & Immun. 61(8): 3496-3502 (Aug. 1993), is cited to show one approach to the treatment of endotoxemia, which is the administration of chylomicrons. Chylomicrons, however, are similar to VLDLs, LDLs, and HDLs in that they contain apolipoproteins. The invention as claimed precludes the administration of these materials.

Harris et al., "Chylomicrons Alter The Fate of Endotoxin Decreasing Tumor Necrosis Factor Release And Preventing Death", J. Clin Invest. 91: 1028-1034 (March 1993) is to the same end as the Read reference, supra.

Eichbaum et al., "Chylomicrons Can Inhibit Endotoxin Activity In Vitro", J. Surg. Res. 51(5): 413-416 (11-91) also shows the effect of chylomicrons, but in an in vitro model.

Feingold et al., "Endotoxin Rapidly Induces Changes In Lipid Metabolism That Produce Hypertriglyceridemia: Low Doses Stimulated

Hepatic Triglyceride Production While High Doses Inhibit Clearance", J. Lipid Res. 33: 1765-1776 (1992), observed the effect alluded to in the reference title. The reference does not suggest how to treat endotoxemia; rather, the mechanism by which LPS acts was studied, and is discussed.

Harris et al., "Detection of Endotoxin In Triglyceride Rich Lipoproteins In Vitro", J. Lab. Clin. Med. 118: 186-193 (1991) involves a study to determine if materials, such as the nutrient supplement SOYACAL, are contaminated with endotoxin. The investigators theorized that contaminating endotoxin might not be noticed due to some inhibiting material. The investigators concluded that the lipoproteins per se did not inhibit endotoxemia, nor did the SOYACAL (page 188, second column). When plasma was added, however, there was inhibition. The further conclusion, at 190, was that, in vitro, triglyceride rich lipoprotein could inhibit detection of endotoxin. There is no suggestion that an in vivo therapeutic effect could be gained from the lipids alone.

Harris et al., "Human Very Low Density Lipoproteins and Chylomicrons Can Protect Against Endotoxin Induced Death In Mice", J. Clin. Invest. 86: 696-702 (9/90) describe comparative studies at 698 (figure 1), using SOYACAL. The doses are not such that they would impinge on the claimed subject matter. Specifically, the reference speaks in terms of administering triglycerides, but does not mention phospholipids. There is simply no way to determine how

much phospholipid is present in the compositions. Using the model disclosed in the specification in Example 8 (page 19), one would conclude that toxicity would result if sufficient SOYACAL were administered to provide an effective phospholipid dose.

Farmer et al., "Hyper lipoproteinemia and Pancreatitis", Am. J. Med. 54: 161-1165 (1973) is an early paper explaining the risk of high lipid levels, and their link to pancreatitis.

Maranhao et al., "Metabolic Behavior in Rats of a Nonprotein Microemulsion Resembling Low Density Lipoprotein", Lipids 28(8): 691-695 (1993) teaches an emulsion which contains phosphatidylcholine, cholesteryl oleate, and triolein. Note page 691, second column. Also note the percentages set forth at page 693, first column. The neutral lipids are well below what is claimed.

Miller and Small, "Structure of Triglyceride-Rich Lipoproteins: An Analysis of Care & Surface Phases" in Gotto, Jr., ed. Plasma Lipoproteins (Elsevier Science Publishers. 1987), p. 1-69, is an extensive analysis of the composition of lipoproteins. The most relevant information will be found at pages 18-32. Various triglyceride containing lipoproteins are discussed. By definition, a lipoprotein is not protein free. Emulsions of triolein, lecithin and water, and triolein, cholesterol, lecithin and water are discussed at page 19, e.g. Examination of the emulsions discussed

therein, however, will show that they do not describe or suggest the claimed subject matter.

It is believed that the cited references do not teach or suggest what is claimed, and a holding to that end is urged.

Respectfully submitted,

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